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MEMORANDUM

SUBJECT: **Ipflufenoquin:** Addendum of the Ecological Risk Assessment for Section 3 New Chemical Registration

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The Environmental Fate and Effects Division (EFED) has completed an addendum to the ecological risk assessment in support of the Section 3 registration decision for the proposed new active ingredient, ipflufenoquin.

This addendum to the ipflufenoquin new chemical ecological risk assessment contains additional evaluations of the potential toxicity of ipflufenoquin to terrestrial plants, in context of the lack of definitive NOAEC noted in the ecological risk assessment. These evaluations do

not change the risk conclusions for any taxa, except for listed terrestrial plants, for which the previous assessment did not make effect determinations while this addendum reaches No Effect determinations for both listed terrestrial plants and listed species that have obligate relationships to terrestrial plants for pollination, prey, habitat or dispersal.

EPA's risk assessments are conducted using a tiered approach, beginning with conservative, tier 1 assumptions such as: (1) assuming that a terrestrial animal eats 100% of its diet as contaminated food sources from a pesticide-treated area; (2) exposure residues are based on upper bound contamination levels from a spray application applied at maximum application rates, maximum number of applications, and minimum application intervals; (3) use of chronic effects thresholds that are known to result in no adverse effects on survival, growth or reproductive endpoints for surrogate taxa. EPA relied on these assumptions to produce a conservative and generic screening assessment for risks to non-target species.

With this approach, EPA relied on risk quotients to screen out listed species at the taxa level if the risk quotients did not exceed the listed-species level of concern. This is a level below which EPA does not anticipate discernable effects. Conversely, risk quotients above this level help EPA identify listed species for which there are potential risk concerns and additional analysis may be needed. EPA calculates these taxa-based risk quotients by dividing conservative estimates of exposure by toxicity endpoints. EPA then compares the risk quotients to established levels of concern to represent effects representing no discernable effects (for acute exposures, effects are lower than background control mortality; for chronic effects, effects represent no observed adverse effects concentrations or levels). EPA's risk quotients are used to assess potential effects from acute and chronic exposures to listed species as well as impacts that may occur from effects to the prey, pollination, habitat and/or dispersal (PPHD) of listed species. Generic taxa based risk quotients are also used to represent potential impacts to PPHD.

If the screening assessment did not identify potential effects for a taxon based on these assumptions (including both direct effects and effects to PPHD), then EPA is confident that no discernable effects to listed species within that taxon will occur. In that scenario, EFED concludes that No Effect determinations for listed species in that taxon are appropriate.

Based on the results from the original ecological risk assessment in support of the Section 3 registration decision for the new active ingredient, ipflufenoquin, and the analysis presented in this addendum, EFED has concluded that No Effect determinations can be made for all listed species and designated critical habitats.

1) Ipflufenoquin Non-Target Plant Listed Species and Obligates Evaluation

The Section 3 New Chemical Ecological Risk Assessment (ERA; USEPA, 2021; D455013) identified that effect determinations could not be made at that time for listed terrestrial plants or for those listed species that have an obligate relationship to a terrestrial plant species or critical habitat with defined Principle Constituent Elements (PCEs) or Physical or Biological Features (PBFs) that indicate obligate relationships to a specific terrestrial plant species. Potential effects to listed plant species were not fully evaluated in the ERA due to statistically significant (p<0.05) effects in the Tier I seedling emergence test (MRID 50921087) to onion, wheat and soybean. All observed effects, as compared to the control, were less than 25%, with an 11% effect on soybean height and 10%-13% effects on dry biomass for these three species at an application rate of 0.09 lbs a.i./A. Therefore, a definitive no observed adverse effect concentration (NOAEC) was not established for those three test species. No effects were observed in the submitted vegetative vigor study (NOAEC = 0.09 lb a.i./A, highest concentration tested). Given these statistically significant, but relatively low inhibitions in the seedling emergence study, EFED investigated whether there were available lines of evidence that provide sufficient evidence for EFED to make Effects Determinations for terrestrial plants. These lines of evidence included: 1) the historical control variability for each endpoint that was determined to be significantly different in the Tier I tests, 2) available data on similar registered quinoline fungicides and 3) the difference between the test concentration compared to the proposed registered application rate and potential exposure concentrations.

1. Historical Plant Variability in Controls

USEPA recently released an analysis of variability in dry weight and height data for historical control plants of commonly tested species in vegetative vigor and seedling emergence studies as part of the biological effects (BE) determinations for the Atrazine[1], Propazine[2], Simazine[3] and Glyphosate[4] Herbicide BEs. This analysis, titled as the "PVP analysis" is available online as attachment 1-5 in the Chapter 1 Problem Formulation for each BE.

The PVP analysis determined minimum detectable difference in historical control plants expressed as a percentage change (MDD%) which indicates the likelihood of finding a specific size effect statistically significant from a hypothesis test (*e.g.* Dunnett, Williams, etc.). The MDD is analogous to a power calculation and can estimate the size of the effect that can be detected from a given sample. For example, if the MDD% = 15%, then it is unlikely to be able to detect or estimate an effect of less than 15%, but likely able to estimate an effect of 15% or more. The MDD of historical control plants is presented below along with the comparable statistically significant differences that were detected in the Tier I seedling emergence study with ipflufenoquin.

[1] https://www.epa.gov/endangered-species/draft-national-level-listed-species-biological-evaluation-atrazine
[2] https://www.epa.gov/endangered-species/draft-national-level-listed-species-biological-evaluation-propazine
[3] https://www.epa.gov/endangered-species/draft-national-level-listed-species-biological-evaluation-simazine
[4] https://www.epa.gov/endangered-species/draft-national-level-listed-species-biological-evaluation-glyphosate

Table 1. Comparison of observed statistically significant decreases in treated versus control plants in Tier I seedling emergence test (MRID 50921087) compared with the minimum detectable difference among historical control plant populations.

Test Species	Inhibition of Biomass in Ipflufenoquin Study (%)	Biomass MDD%	Inhibition of Plant Height in Ipflufenoquin Study (%)	Plant Height MDD%
Soybean	10.0	16.1	10.7	14.1
Wheat	11.4	16.5	NS	N/A
Onion	13.5	28.8	NS	N/A

NS = No statistically significant differences detected between treatment and control plants
N/A = Not applicable

As observed from **Table 1**, in each case where a statistically significant difference was detected in the Tier I study with ipflufenoquin, the minimum detectable percent difference among historical control plants is greater than the percent effect observed in the Tier I study. This suggests that EFED's confidence that the statistically significant differences observed in the Tier I seedling emergence test represent actual treatment-related effects is fairly limited. EFED further notes that the PVP analysis in historical controls plants suggested the use of an IC_{20} and IC_{10} estimates for dry weight (biomass) and height, respectively, when a definitive NOAEC is not available. Although ICx estimates cannot be derived from Tier I limit dose studies such as the available seedling emergence study for ipflufenoquin, EFED notes that (in comparison to the suggested ICx thresholds recommended by the PVP analysis) the effects on seedling emergence for these species at the limit dose were well below 20% for biomass and were at 10% for height.

2) Comparison of Ipflufenoquin with other Registered Quinoline Fungicides

Registered quinoline fungicides in the United States include ethoxyquin, quinoxyfen and 8-hydroxyquinoline sulfate. As ethoxyquin and 8-hydroxyquinoline are restricted to indoor uses, terrestrial plant data are not available for these active ingredients. However, quinoxyfen plant data are available. Quinoxyfen and ipflufenoquin share a quinoline double ring as a backbone (**Fig. 1**) and share similar fungicidal activity. The quinoxyfen PRA (USEPA, 2017; D434386) notes that none of the ten tested plant species in the seedling emergence test (MRID 45360607) showed a phytotoxic response following application up to 0.5 lbs a.i./A. (an application rate more than 5x higher than the tested rate for ipflufenoquin), while of the ten tested plant species in the quinoxyfen vegetative vigor test (MRID 45360607), only one (cucumber) had observed phytotoxic effects with a NOAEC and LOAEC of 0.064 and 0.136 lbs a.i./A, respectively, which compares reasonably well with the ipflufenoquin vegetative vigor data (NOAEC and LOAEC of 0.09 and >0.09 lb a.i./A, respectively).

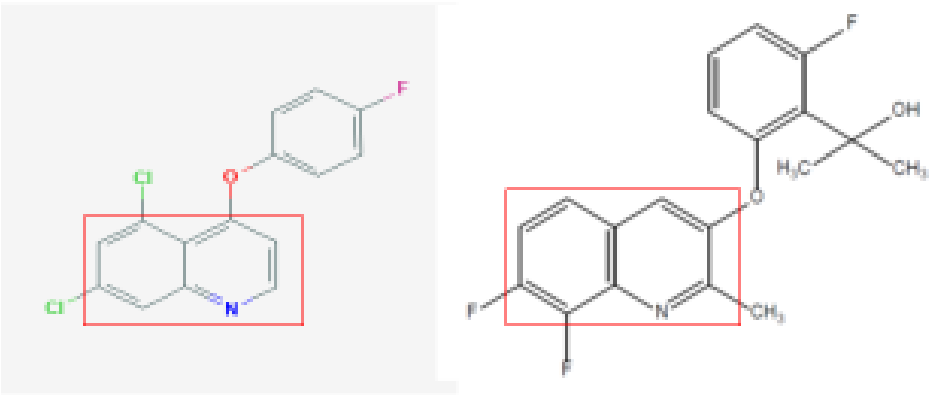

Fig. 1 Chemical Structures for quinoxyfen (left) and ipflufenoquin (right). Red boxes highlight the quinoline double ring underlying each structure.

3) Consideration of Ipflufenoquin Tested Rates vs. Potential Exposure Conditions

EFED notes that the tested rate in the ipflufenoquin seedling emergence study was 0.09 lbs a.i./A, which is approximately 25% higher than the maximum proposed single application rate of 0.065 lbs a.i./A. To some extent, the seedling emergence test design is also inherently conservative relative to field conditions. Exposure in the seedling emergence test involves exposing the soil with test material as would be done for targeted in-field plants. However, potential risk to non-target off-field plants would presumably only receive a fraction of the pesticide in run-off (and/or spray drift) from the treated field. Based on ipflufenoquin's solubility and use patterns, TerrPlant modeling determined that EECs in nearby dry and semi-aquatic areas would be 0.00455 and 0.0163 lbs/A, respectively, which are 20x and 5.5x lower than the tested rate, respectively. Given TerrPlant's assumptions including 100% application efficiency in ground and aerial applications, runoff fractions solely dependent on the solubility of the active ingredient (*i.e.* not considering other relevant transport properties that influence pesticide movement through the soil or in eroded soil or the potential degradation of the active ingredient), and 10-to-1 ratio of target area to semi-aquatic non-target areas, these estimated off-field exposure values are likely highly conservative.

Integration of Available Lines of Evidence

Off-field Listed Plant Species Effect Determinations

Based on multiple lines of evidence, ipflufenoquin applications at the maximum registered application rate of 0.065 lbs a.i./A appear to be unlikely to pose risk to off-field listed terrestrial plant species. These lines of evidence include that the apparent phytotoxic effects observed in the ipflufenoquin seedling emergence study were limited to levels that appear to be within estimates of historical control plant variability, that another registered compound in the chemical class with a similar chemical structure did not have phytotoxic effects on seedling emergence at rates approximately an order of magnitude above the registered rate for ipflufenoquin and the conservatism of the seedling emergence test (higher tested application rate than registered, tested exposure representative of on-field target plants, compared to off-field listed plant species presence, actual NOAEC needing to be at least 5.5x below tested rate to result in potential risk concerns). Therefore, No Effect determinations are made to off-field listed plant species.

On-Field Listed Plant Species Effect Determinations

EFED risk assessment has typically not assessed risk to non-target plants on the field with the assumption that non-target plants will not be present on the field. EPA's pesticide risk assessment Overview document (USEPA, 2004) also notes: "Listed plants do not occur in cultivated fields. EPA acknowledges that they can get to such fields, and even germinate there. But the cultivation will not allow the plant to continue to exist there even in the absence of pesticide use. Therefore, the assumption is made that any effects to listed plants occur outside the treated field." However, recent endangered species risk assessments (*e.g.* USEPA, 2020; D459792 on the use of herbicides on herbicide-tolerant genetically modified (GMO) crops have considered the potential for listed plant species to be on the treated field. However, the first two lines of evidence described above for off-field listed plant species effects determinations (historical plant variability in relation to ipflufenoquin test results and test results from the similar chemical, quinoxyfen) remain the same for any potential on-field listed plant species. For the third line of evidence, while exposures on-field are certainly higher than the modeled exposures off-field, they would still be approximately 25% below the tested application rate in the ipflufenoquin seedling emergence test. Based on these lines of evidence, EFED also determines a No Effect determination for any listed on-field listed plant species from ipflufenoquin applications. At this time, no additional terrestrial plant data is needed to reach effect determinations for terrestrial plants. Should higher application rates be proposed in the future, EFED may need to reconsider whether additional data may be necessary to maintain the No Effect determinations.

Overall Conclusions

As the lines of evidence described above have resulted in No Effect determinations for all listed plant taxa and No Effect determinations had previously been made (USEPA, 2021) for all other listed taxa and for all designated critical habitat except for those listed species with defined PCEs/PBFs that indicated an obligate relationship to a specific listed terrestrial plant species, EPA now concludes that No Effect determinations can be made for all listed taxa and for all designated critical habitats.

References

USEPA. 2017. Registration Review: Preliminary Environmental Fate and Ecological Risk Assessment for Quinoxyfen. D434386. Environmental Fate and Effects Division. Office of Pesticide Programs. U.S. Environmental Protection Agency.

USEPA. 2020. 2020 Ecological Assessment of Dicamba Use on Dicamba-Tolerant (DT) Cotton and Soybean Including Effects Determinations for Federally Listed Threatened and Endangered Species. D459792, 459793, 459794. Environmental Fate and Effects Division. Office of Pesticide Programs. U.S. Environmental Protection Agency. October 26, 2020.

USEPA. 2021. Ipflufenoquin: Ecological Risk Assessment for Section 3 New Chemical Registration. D455013. Environmental Fate and Effects Division. Office of Pesticide Programs. U.S. Environmental Protection Agency.